

Sequence Listing

<110> Henry B. Lowman, Leonard G. Presta, Paula M. Jardieu, John Lowe

5 <120> Anti-IgE Antibodies and Method of Improving Polypeptides

<130> P1123R1

<140> US 09/109,207

10 <141> 1998-06-30

<150> US 60/051,554

<151> 1997-07-03

15 <160> 44

<210> 1

<211> 6127

<212> DNA

20 <213> Artificial

<220>

<221> Artificial

<222> 1-6127

25 <223> Expression plasmid

<400> 1

gaattcaact tctccatact ttggataagg aaatacagac atgaaaaatc 50

30 tcattgctga gttgttattt aagcttgccc aaaaagaaga agagtcgaat 100

gaactgtgtg cgcaggtaga agctttggag attatcgtca ctgcaatgct 150

35 tcgcaatatg gcgcaaaatg accaacagcg gttgattgat caggtagagg 200

gggcgctgta cgaggtaaag cccgatgcc a gattcctga cgacgatacg 250

gagctgctgc gcgattacgt aaagaagtta ttgaagcatc ctcgtcagta 300

40 aaaagttaat cttttcaaca gctgtcataa agttgtcacg gccgagactt 350

atagtcgctt tgtttttatt ttttaatgta tttgtaacta gaattcgagc 400

45 tcgggtaccg gggatcctct cgagggttag gtgattttat gaaaaagaat 450

atcgcatctt ttcttgcatc tatgttcgtt ttttctattg ctacaaacgc 500

gtacgctgat atccagctga cccagtcgcc gagtcacctg tccgcctctg 550

50 tgggcgatag ggtcaccatc acctgccgtg ccagtcagag cgtcgattac 600

gaaggtgata gctacctgaa ctggatatcaa cagaaaccag gaaaagctcc 650

55 gaaactactg atttacgcgg cctcgtaact ggagtcctgga gtcccttctc 700

gcttctctgg atccggttct gggacggatt tcaactctgac catcagcagt 750

ctgcagccag aagacttcgc aacttattac tgtcagcaaa gtcacgagga 800

60 tccgtacaca tttggacagg gtaccaaggt ggagatcaaa cgaactgtgg 850

ctgcaccatc tgtcttcac ttcccgcac ctgatgagca gttgaaatct 900

ggaactgctt ctgttggtg cctgctgaat aacttctatc ccagagaggc 950
 5 caaagtacag tggaagggtg ataacgccct ccaatcgggt aactcccagg 1000
 agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 1050
 accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg 1100
 10 cgaagtcacc catcagggcc tgagctcgcc cgtcaciaag agcttcaaca 1150
 ggggagagtg ttaagctgat cctctacgcc ggacgcatcg tggccctagt 1200
 acgcaagttc acgtaaaaag ggtatctaga ggttgagggtg attttatgaa 1250
 15 aaagaatata gcattttctt ttgcatctat gttcgttttt tctattgcta 1300
 caaacgcgta cgctgagggt cagctgggtg agtctggcgg tggcctgggtg 1350
 20 cagccagggg gctcactccg tttgtcctgt gcagtttctg gctactccat 1400
 cacctccgga tacagctgga actggatccg tcaggccccg ggtaagggcc 1450
 tggaatgggt tgcctcgatt acgtatgacg gatcgactaa ctataaccct 1500
 25 agcgtcaagg gccgtatcac tataagtcgc gacgattcca aaaacacatt 1550
 ctacctgcag atgaacagcc tgcgtgctga ggacactgcc gtctattatt 1600
 30 gtgctcgagg cagccactat ttcggctcact ggcaacttcgc cgtgtgggggt 1650
 caaggaaccc tggtcaccgt ctccctcggcc tccaccaagg gcccatcgggt 1700
 cttcccccta gcacctcct ccaagagcac ctctgggggc acagcggccc 1750
 35 tgggctgcct ggtcaaggac tacttccccg aaccgggtgac ggtgtcgtgg 1800
 aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca 1850
 40 gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg cctccagca 1900
 gcttgggcac ccagacctac atctgcaacg tgaatcacia gccagcaac 1950
 accaagggtg acaagaaagt tgagcccaa tcttgtgaca aaactcacac 2000
 45 cttagagtggc ggtggctctg gttccgggtga ttttgattat gaaaagatgg 2050
 caaacgctaa taagggggct atgaccgaaa atgccgatga aaacgcgcta 2100
 50 cagtctgacg ctaaaggcaa acttgattct gtcgtactg attacgggtgc 2150
 tgctatcgat ggtttcattg gtgacgtttc cggccttgct aatggtaatg 2200
 55 gtgctactgg tgattttgct ggctctaatt cccaaatggc tcaagtcgggt 2250
 gacggtgata attcaccttt aatgaataat ttccgtcaat atttaccttc 2300
 cctccctcaa tcggttgaat gtcgcccttt tgtctttagc gctggtaaac 2350
 60 catatgaatt ttctattgat tgtgacaaaa taaacttatt ccgtgggtgc 2400
 tttgcgtttc ttttatatgt tgccaccttt atgtatgtat tttctacgtt 2450

<220>

<221> Artificial

<222> 1-121

5 <223> F(ab) sequence derived from MAE11

<400> 3

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

10 Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
20 25 30

15 Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
35 40 45

Leu Glu Trp Val Ala Ser Ile Thr Tyr Asp Gly Ser Thr Asn Tyr
50 55 60

20 Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
65 70 75

Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90

25 Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
95 100 105

30 Trp His Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
110 115 120

Ser

35 <210> 4

<211> 121

<212> PRT

<213> Homo sapiens

40 <220>

<221> unsure

<222> 30, 104-108

<223> unknown amino acid

45 <400> 4

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

50 Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Xaa
20 25 30

Ser Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
35 40 45

55 Leu Glu Trp Val Ala Val Ile Ser Asn Gly Ser Asp Thr Tyr Tyr
50 55 60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
65 70 75

60 Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Ser Arg Phe Phe Xaa Xaa
 95 100 105
 5 Xaa Xaa Xaa Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 110 115 120
 Ser
 10
 <210> 5
 <211> 111
 <212> PRT
 <213> Mus musculus
 15
 <400> 5
 Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu
 1 5 10 15
 20 Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp
 20 25 30
 Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly
 35 40 45
 25 Gln Pro Pro Ile Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Gly Ser
 50 55 60
 Glu Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
 65 70 75
 30 Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Phe
 80 85 90
 35 Tyr Cys Gln Gln Ser His Glu Asp Pro Tyr Thr Phe Gly Ala Gly
 95 100 105
 Thr Lys Leu Glu Ile Lys
 110
 40
 <210> 6
 <211> 111
 <212> PRT
 <213> Artificial
 45
 <220>
 <221> Artificial
 <222> 1-111
 <223> F(ab) light chain sequence derived from MAE11
 50
 <400> 6
 Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
 1 5 10 15
 55 Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Asp
 20 25 30
 Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly
 35 40 45
 60 Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu Ser
 50 55 60

| | | | | |
|----|---|-----|-----|-----|
| | Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe | 65 | 70 | 75 |
| 5 | Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr | 80 | 85 | 90 |
| | Tyr Cys Gln Gln Ser His Glu Asp Pro Tyr Thr Phe Gly Gln Gly | 95 | 100 | 105 |
| 10 | Thr Lys Val Glu Ile Lys | 110 | | |
| | <210> 7 | | | |
| 15 | <211> 111 | | | |
| | <212> PRT | | | |
| | <213> Homo sapiens | | | |
| | <220> | | | |
| 20 | <221> unsure | | | |
| | <222> 33-34 | | | |
| | <223> unknown amino acid | | | |
| | <400> 7 | | | |
| 25 | Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val | 1 | 5 | 10 |
| | | | | 15 |
| | Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Asp | 20 | 25 | 30 |
| 30 | Ile Ser Xaa Xaa Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly | 35 | 40 | 45 |
| | | | | |
| 35 | Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser | 50 | 55 | 60 |
| | | | | |
| | Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe | 65 | 70 | 75 |
| 40 | Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr | 80 | 85 | 90 |
| | Tyr Cys Gln Gln Tyr Asn Ser Leu Pro Tyr Thr Phe Gly Gln Gly | 95 | 100 | 105 |
| 45 | Thr Lys Val Glu Ile Lys | 110 | | |
| | <210> 8 | | | |
| 50 | <211> 114 | | | |
| | <212> PRT | | | |
| | <213> Artificial | | | |
| | <220> | | | |
| 55 | <221> Artificial | | | |
| | <222> 1-114 | | | |
| | <223> Light chain sequence derived from MAE11 | | | |
| | <400> 8 | | | |
| 60 | Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val | 1 | 5 | 10 |
| | | | | 15 |

<221> Artificial
 <222> 1-114
 <223> Light chain sequence derived from MAE11

5 <400> 10
 Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
 1 5 10 15
 Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Asp
 10 20 25 30
 Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly
 35 40 45
 15 Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu Ser
 50 55 60
 Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
 65 70 75
 20 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
 80 85 90
 Tyr Cys Gln Gln Ser His Glu Asp Pro Tyr Thr Phe Gly Gln Gly
 25 95 100 105
 Thr Lys Val Glu Ile Lys Arg Thr Val
 110

30 <210> 11
 <211> 114
 <212> PRT
 <213> Artificial

35 <220>
 <221> Artificial
 <222> 1-114
 <223> Heavy chain sequence derived from MAE11

40 <400> 11
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
 45 20 25 30
 Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
 35 40 45
 50 Leu Glu Trp Val Ala Ser Ile Lys Tyr Ser Gly Glu Thr Lys Tyr
 50 55 60
 Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser
 65 70 75
 55 Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 80 85 90
 Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
 60 95 100 105
 Trp His Phe Ala Val Trp Gly Gln Gly

5 <210> 12
 <211> 114
 <212> PRT
 <213> Artificial

10 <220>
 <221> Artificial
 <222> 1-114
 <223> Heavy chain sequence derived from MAE11

15 <400> 12
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
 20 25 30
 Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
 35 40 45
 Leu Glu Trp Val Ala Ser Ile Thr Tyr Asp Gly Ser Thr Asn Tyr
 50 55 60
 Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser
 65 70 75
 Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 80 85 90
 Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
 95 100 105
 35 Trp His Phe Ala Val Trp Gly Gln Gly
 110

40 <210> 13
 <211> 218
 <212> PRT
 <213> Artificial

45 <220>
 <221> Artificial
 <222> 1-218
 <223> Light chain sequence derived from MAE11

50 <400> 13
 Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
 1 5 10 15
 Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Asp
 20 25 30
 Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly
 35 40 45
 Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu Ser
 50 55 60
 60 Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
 65 70 75

| | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|
| | Trp | His | Phe | Ala | Val 110 | Trp | Gly | Gln | Gly | Thr 115 | Leu | Val | Thr | Val | Ser 120 |
| 5 | Ser | Ala | Ser | Thr | Lys 125 | Gly | Pro | Ser | Val | Phe 130 | Pro | Leu | Ala | Pro | Ser 135 |
| | Ser | Lys | Ser | Thr | Ser 140 | Gly | Gly | Thr | Ala | Ala 145 | Leu | Gly | Cys | Leu | Val 150 |
| 10 | Lys | Asp | Tyr | Phe | Pro 155 | Glu | Pro | Val | Thr | Val 160 | Ser | Trp | Asn | Ser | Gly 165 |
| | Ala | Leu | Thr | Ser | Gly 170 | Val | His | Thr | Phe | Pro 175 | Ala | Val | Leu | Gln | Ser 180 |
| 15 | Ser | Gly | Leu | Tyr | Ser 185 | Leu | Ser | Ser | Val | Val 190 | Thr | Val | Pro | Ser | Ser 195 |
| 20 | Ser | Leu | Gly | Thr | Gln 200 | Thr | Tyr | Ile | Cys | Asn 205 | Val | Asn | His | Lys | Pro 210 |
| | Ser | Asn | Thr | Lys | Val 215 | Asp | Lys | Lys | Val | Glu 220 | Pro | Lys | Ser | Cys | Asp 225 |
| 25 | Lys | Thr | His | Thr | Cys 230 | Pro | Pro | Cys | Pro | Ala 235 | Pro | Glu | Leu | Leu | Gly 240 |
| | Gly | Pro | Ser | Val | Phe 245 | Leu | Phe | Pro | Pro | Lys 250 | Pro | Lys | Asp | Thr | Leu 255 |
| 30 | Met | Ile | Ser | Arg | Thr 260 | Pro | Glu | Val | Thr | Cys 265 | Val | Val | Val | Asp | Val 270 |
| 35 | Ser | His | Glu | Asp | Pro 275 | Glu | Val | Lys | Phe | Asn 280 | Trp | Tyr | Val | Asp | Gly 285 |
| | Val | Glu | Val | His | Asn 290 | Ala | Lys | Thr | Lys | Pro 295 | Arg | Glu | Glu | Gln | Tyr 300 |
| 40 | Asn | Ser | Thr | Tyr | Arg 305 | Val | Val | Ser | Val | Leu 310 | Thr | Val | Leu | His | Gln 315 |
| | Asp | Trp | Leu | Asn | Gly 320 | Lys | Glu | Tyr | Lys | Cys 325 | Lys | Val | Ser | Asn | Lys 330 |
| 45 | Ala | Leu | Pro | Ala | Pro 335 | Ile | Glu | Lys | Thr | Ile 340 | Ser | Lys | Ala | Lys | Gly 345 |
| 50 | Gln | Pro | Arg | Glu | Pro 350 | Gln | Val | Tyr | Thr | Leu 355 | Pro | Pro | Ser | Arg | Glu 360 |
| | Glu | Met | Thr | Lys | Asn 365 | Gln | Val | Ser | Leu | Thr 370 | Cys | Leu | Val | Lys | Gly 375 |
| 55 | Phe | Tyr | Pro | Ser | Asp 380 | Ile | Ala | Val | Glu | Trp 385 | Glu | Ser | Asn | Gly | Gln 390 |
| | Pro | Glu | Asn | Asn | Tyr 395 | Lys | Thr | Thr | Pro | Pro 400 | Val | Leu | Asp | Ser | Asp 405 |
| 60 | Gly | Ser | Phe | Phe | Leu | Tyr | Ser | Lys | Leu | Thr | Val | Asp | Lys | Ser | Arg |

410

415

420

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
425 430 435

5

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
440 445 450

Lys

10

<210> 15

<211> 218

<212> PRT

15

<213> Artificial

<220>

<221> Artificial

<222> 1-218

20

<223> Light chain sequence derived from MAE11

<400> 15

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

25

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Pro Val Asp
20 25 30

30

Gly Glu Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
35 40 45

Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu Ser
50 55 60

35

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
65 70 75

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
80 85 90

40

Tyr Cys Gln Gln Ser His Glu Asp Pro Tyr Thr Phe Gly Gln Gly
95 100 105

45

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
110 115 120

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
125 130 135

50

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
140 145 150

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
155 160 165

55

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
170 175 180

60

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
185 190 195

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr

200

205

210

Lys Ser Phe Asn Arg Gly Glu Cys
215

5

<210> 16
<211> 451
<212> PRT
<213> Artificial

10

<220>
<221> Artificial
<222> 1-451
<223> Heavy chain sequence derived from MAE11

15

<400> 16
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

20

Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
20 25 30

Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
35 40 45

25

Leu Glu Trp Val Ala Ser Ile Thr Tyr Asp Gly Ser Thr Asn Tyr
50 55 60

30

Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser
65 70 75

Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90

35

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
95 100 105

Trp His Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
110 115 120

40

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
125 130 135

45

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
140 145 150

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
155 160 165

50

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
170 175 180

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
185 190 195

55

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
200 205 210

60

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
215 220 225

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

30

5

Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu Ser
50 55 60

10

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
80 85 90

15

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
110 115 120

20

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Val | Cys | Leu | Leu | Asn | Asn | Phe | Tyr | Pro | Arg | Glu | Ala | Lys | Val |
| | | | | 140 | | | | | 145 | | | | | 150 |

25

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
155 160 165

30

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
185 190 195

35

Lys Ser Phe Asn Arg Gly Glu Cys
215

40

<210> 18

$\langle 211 \rangle \cdot 451$

<212> PRT

45

 $\langle 220 \rangle$

<221> Artificial

<222> 1-451

50

<400> 18

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

55

Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
20 25 30

Leu Glu Trp Val Ala Ser Ile Lys Tyr Ser Gly Glu Thr Lys Tyr

60

18

[illegible]

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
155 160 165

5 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
170 175 180

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
185 190 195

10 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
200 205 210

Lys Ser Phe Asn Arg Gly Glu Cys
215

15 <210> 20
<211> 229
<212> PRT
<213> Artificial

20 <220>
<221> Artificial
<222> 1-229
<223> Heavy chain F(ab) sequence derived from MAE11

25 <400> 20
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

30 Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
20 25 30

Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
35 35 40 45

Leu Glu Trp Val Ala Ser Ile Thr Tyr Asp Gly Ser Thr Asn Tyr
50 55 60

40 Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser
65 70 75

Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90

45 Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
95 100 105

Trp His Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
110 115 120

50 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
125 130 135

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
140 145 150

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
155 160 165

60 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
170 175 180

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 200 205 210

5 Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 215 220 225

Lys Thr His Thr

10 <210> 22
 <211> 248
 <212> PRT
 <213> Artificial

15 <220>
 <221> Artificial
 <222> 1-248
 <223> sFv sequence derived from MAE11

20 <400> 22
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15

25 Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
 20 25 30

Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
 35 40 45

30 Leu Glu Trp Val Ala Ser Ile Thr Tyr Asp Gly Ser Thr Asn Tyr
 50 55 60

Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser
 65 70 75

35 Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 80 85 90

40 Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
 95 100 105

Trp His Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 110 115 120

45 Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly
 125 130 135

Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
 140 145 150

50 Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Pro Val
 155 160 165

55 Asp Gly Glu Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro
 170 175 180

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu
 185 190 195

60 Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
 200 205 210

| | | | | |
|----|---|-----|-----|-------|
| | Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr | 215 | 220 | 225 |
| 5 | Tyr Tyr Cys Gln Gln Ser His Glu Asp Pro Tyr Thr Phe Gly Gln | 230 | 235 | 240 |
| | Gly Thr Lys Val Glu Ile Lys Arg | 245 | | |
| 10 | <210> 23 | | | |
| | <211> 248 | | | |
| | <212> PRT | | | |
| | <213> Artificial | | | |
| 15 | <220> | | | |
| | <221> Artificial | | | |
| | <222> 1-248 | | | |
| | <223> sFv sequence derived from MAE11 | | | |
| 20 | <400> 23 | | | |
| | Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly | 1 | 5 | 10 15 |
| 25 | Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr | 20 | 25 | 30 |
| | Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly | 35 | 40 | 45 |
| 30 | Leu Glu Trp Val Ala Ser Ile Lys Tyr Ser Gly Glu Thr Lys Tyr | 50 | 55 | 60 |
| | Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser | 65 | 70 | 75 |
| 35 | Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp | 80 | 85 | 90 |
| 40 | Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His | 95 | 100 | 105 |
| | Trp His Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser | 110 | 115 | 120 |
| 45 | Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly | 125 | 130 | 135 |
| | Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser | 140 | 145 | 150 |
| 50 | Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Pro Val | 155 | 160 | 165 |
| 55 | Asp Gly Glu Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro | 170 | 175 | 180 |
| | Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu | 185 | 190 | 195 |
| 60 | Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp | 200 | 205 | 210 |

Lys Ser Phe Asn Arg Gly Glu Cys
215

5 <210> 25
<211> 233
<212> PRT
<213> Artificial

10 <220>
<221> Artificial sequence
<222> 1-233
<223> Heavy chain F(ab)'2 sequence derived from MAE11

15 <400> 25
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15
Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
20 20 25 30
Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
35 40 45
Leu Glu Trp Val Ala Ser Ile Thr Tyr Asp Gly Ser Thr Asn Tyr
25 50 55 60
Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser
65 70 75
30 Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90
Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
35 95 100 105
Trp His Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
110 115 120
40 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
125 130 135
Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
140 145 150
45 Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
155 160 165
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
170 175 180
50 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
185 190 195
55 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
200 205 210
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
215 220 225
60 Lys Thr His Thr Cys Pro Pro Cys
230

<210> 26
 <211> 233
 <212> PRT
 <213> Artificial

5

<220>
 <221> Artificial
 <222> 1-233
 <223> Heavy chain F(ab)'2 sequence derived from MAE11

10

<400> 26
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15

15

Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Tyr Ser Ile Thr
 20 25 30

20

Ser Gly Tyr Ser Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly
 35 40 45

Leu Glu Trp Val Ala Ser Ile Lys Tyr Ser Gly Glu Thr Lys Tyr
 50 55 60

25

Asn Pro Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asp Ser
 65 70 75

Lys Asn Thr Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 80 85 90

30

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser His Tyr Phe Gly His
 95 100 105

Trp His Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 110 115 120

35

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
 125 130 135

40

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 140 145 150

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 155 160 165

45

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 170 175 180

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 185 190 195

50

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 200 205 210

55

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 215 220 225

Lys Thr His Thr Cys Pro Pro Cys
 230

60

<210> 27
 <211> 45
 <212> DNA

<213> Artificial
 <220>
 <221> Artificial
 5 <222> 1-45
 <223> Stop-Template Oligos for First-Round Mutagenesis
 <400> 27
 10 acctgccgtg ccagttaata agtctaataa gaaggtgata gctac 45
 <210> 28
 <211> 46
 <212> DNA
 <213> Artificial
 15 <220>
 <221> Artificial
 <222> 1-46
 <223> Stop-Template Oligos For First-Round Mutagenesis
 20 <400> 28
 gccagtcaga gcgtctaata ataagggtga agctacctga actggt 46
 <210> 29
 25 <211> 50
 <212> DNA
 <213> Artificial
 <220>
 30 <221> Artificial
 <222> 1-50
 <223> Stop-Template Oligos For First-Round Mutagenesis
 <400> 29
 35 tgtgctcgag gcagctaata ataagggttaa tggtaattcg ccgtgtgggg 50
 <210> 30
 <211> 43
 <212> DNA
 40 <213> Artificial
 <220>
 <221> Artificial
 <222> 1-43
 45 <223> Stop-Template Oligos For First-Round Mutagenesis
 <400> 30
 gaaactactg atttactaat aataataact ggagtctgga gtc 43
 <210> 31
 50 <211> 53
 <212> DNA
 <213> Artificial
 55 <220>
 <221> Artificial
 <222> 1-53
 <223> Stop-Template Oligos For First-Round Mutagenesis
 60 <400> 31
 cttattactg tcagcaaagt taataataac cgtaaactt tggacagggt 50

acc 53

<210> 32
 <211> 46
 5 <212> DNA
 <213> Artificial

<220>
 <221> Artificial
 10 <222> 1-46
 <223> Stop-Template Oligos For First-Round Mutagenesis

<400> 32
 15 gtcctgtgca gtttcttaat aataataata atccggatac agctgg 46

<210> 33
 <211> 45
 <212> DNA
 <213> Artificial

20 <220>
 <221> Artificial
 <222> 1-45
 <223> Stop-Template Oligos For First-Round Mutagenesis

25 <400> 33
 gcctactcca tcacctaata ataaagctga aactggatcc gtcag 45

<210> 34
 30 <211> 53
 <212> DNA
 <213> Artificial

<220>
 35 <221> Artificial
 <222> 1-53
 <223> Stop-Template Oligos For First-Round Mutagenesis

<400> 34
 40 gggttgcatc gatttaataa taaggataaa cttaatataa ccctagcctc 50

aag 53

<210> 35
 45 <211> 48
 <212> DNA
 <213> Artificial

<220>
 50 <221> Artificial
 <222> 1-48
 <223> Stop-Template Oligos For First-Round Mutagenesis

<400> 35
 55 aagccggctcg acaggtaata agattaatac taaaactggt atcaacag 48

<210> 36
 <211> 45
 <212> DNA
 60 <213> Artificial

<220>

<221> Artificial
 <222> 1-45
 <223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

5 <220>
 <221> unsure
 <222> 16-17, 19-20, 25-26, 28-29
 <223> unknown base

10 <400> 36
 acctgccgtg ccagtnnsnn sgtcnnsnns gaaggtgata gctac 45
 <210> 37
 <211> 45

15 <212> DNA
 <213> Artificial
 <220>
 <221> Artificial
 <222> 1-45
 <223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

20 <220>
 <221> unsure
 <222> 16-17, 19-20, 22, 28-29
 <223> unknown base

25 <400> 37
 gccagtcaga gcgtcnnsnn snssggttnns agctacctga actgg 45
 <210> 38
 <211> 50
 <212> DNA
 <213> Artificial

30 <220>
 <221> Artificial
 <222> 1-50
 <223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

35 <220>
 <221> unsure
 <222> 16-17, 19-20, 22-23, 28-29, 34-35
 <223> unknown base

40 <400> 38
 tgtgtcgag gcagcnnsnn snssggttnns tggnnsttcg ccgtgtgggg 50
 <210> 39
 <211> 43
 <212> DNA
 <213> Artificial

45 <220>
 <221> Artificial
 <222> 1-43
 <223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

50 <220>
 <221> unsure
 <222> 17-18, 20-21, 23-24, 26-27
 <223> unknown base

55 <220>
 <221> unsure
 <222> 17-18, 20-21, 23-24, 26-27
 <223> unknown base

60 <220>
 <221> unsure
 <222> 17-18, 20-21, 23-24, 26-27
 <223> unknown base

<400> 39
 gaaactactg atttacnnsn nsnnsnnsct ggagtctgga gtc 43

5 <210> 40
 <211> 53
 <212> DNA
 <213> Artificial

10 <220>
 <221> Artificial
 <222> 1-53
 <223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

15 <220>
 <221> unsure
 <222> 21-22, 24-25, 27-28, 33-34
 <223> unknown base

20 <400> 40
 cttattactg tcagcaaagt nsnnsnnsnc cgnsacatt tggacagggt 50
 acc 53

25 <210> 41
 <211> 46
 <212> DNA
 <213> Artificial

30 <220>
 <221> Artificial
 <222> 1-46
 <223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

35 <220>
 <221> unsure
 <222> 17-18, 20-21, 23-24, 26-27, 29-30
 <223> unknown base

40 <400> 41
 gtctctgtgca gtttctnnsn nsnnsnnsnn stccggatac agctgg 46

<210> 42
 <211> 51

45 <212> DNA
 <213> Artificial

<220>
 <221> Artificial

50 <222> 1-51
 <223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

<220>
 <221> unsure

55 <222> 22-23, 25-26, 28-29, 34-35
 <223> unknown base

<400> 42
 gtttctggct actccatcac cnnsnnsnns agcnnsaact ggatccgtca 50

60 g 51

<210> 43
<211> 53
<212> DNA
<213> Artificial

5

<220>
<221> Artificial
<222> 1-53
<223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

10

<220>
<221> unsure
<222> 15-16, 18-19, 21-22, 27-28, 33-34
<223> unknown base

15

<400> 43
gggttgcatc gattnnsnns nnsaggannsa ctnnstataa ccctagcgtc 50

aag 53

20

<210> 44
<211> 48
<212> DNA
<213> Artificial

25

<220>
<221> Artificial
<222> 1-48
<223> Library-Specific, Degenerate Oligos For Second Round Mutagenesis

30

<220>
<221> unsure
<222> 16-17, 19-20, 25-26, 31-32
<223> unknown base

35

<400> 44
aagccggtcg acaggnsnn sgatnnstac nnsaactggt atcaacag 48